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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/209,023	12/10/1998	VIRGINIA E. PATON	P1256R3	8941

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	30

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/209,023	PATON ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,12,13 and 34-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-9,12,13 and 34-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *28* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed August 25, 2003 is acknowledged. Claim 1 was amended Claims 1, 4-9, 12, 13 and 34-38 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. The Information Disclosure Statements of 9/6/2001, 4/10/2002, 6/3/2002 and 6/17/2002 are present in the file; copies of signed PTO-1449 forms are attached. The references have been considered, ~~except for some of the references listed in the IDS of 6/3/2002, which were not present in the file. The PTO-1449 form for the IDS filed 1/31/2002 is not present in the file, and the references do not appear to be either.~~ The references cited in the IDS filed 6/13/2003 have been considered.

AEH 12/9/03

Claim Rejections Withdrawn:

4. The rejection of claims 1, 4-9, 12, 13, 34-36 and 38 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is withdrawn in view of the amendment to claim 1, removing the phrase "without increase in overall adverse events, compared to therapy with gemcitabine alone".

5. The rejection of claims 1, 4-9, 12, 13, 34-36 and 38 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to claim 1, removing the phrase "without increase in overall adverse events, compared to therapy with gemcitabine alone".

Art Rejections Reinstated:

6. Claims 1, 4-9, 12-13, 34-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baselga et al.**, Oncology, Vol 11, No 3, March 1997, **Norton**, Seminars in Oncology, Vol 24, No 4, Suppl 10, August 1997, **Lippman et al**, US Patent 5,578,482, November 26, 1996, **Hynes et al.** Biochemica et Biophysica Acta 1198, 1994, or **Arakawa et al**, US Patent 5,783,186, in view of **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.**, European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al.** Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al.**, Cancer Research Vol. 56, pages 794-801, 1996. In view of the amendment to claim 1, the claimed inventions are obvious over the prior art.

7. Claims 1, 4-9 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al., US Patent 5,770,195, and further in view of Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European

Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or Carmichael et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or Tsai et al., Cancer Research Vol. 56, pages 794-801, 1996. In view of the amendment to claim 1, the claimed inventions are obvious over the prior art.

8. Claims 1, 4-9, 12-13 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baselga et al, Journal of Clinical Oncology, Vol 14, No 3, March 1996, in view of Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or Carmichael et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or Tsai et al., Cancer Research Vol. 56, pages 794-801, 1996, and further in view of in view of Hynes et al, Biochimica et Biophysica Acta, 1994, page 178. In view of the amendment to claim 1, the claimed inventions are obvious over the prior art.

9. Claims 1, 4-9 12-13, 34-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baselga et al., Journal of Clinical Oncology, Vol 14, No 3, March 1996 (Baselga I), Baselga et al., Oncology, Vol 11, No 3, March 1997 (Baselga II), Norton, Seminars in Oncology, Vol 24, No 4, Suppl 10, August 1997, Lippman et al, US Patent 5,578,482, November 26, 1996, Hynes et al. Biochemica et Biophysica Acta 1198, 1994, or Arakawa et al,

US Patent 5,783,186 or Hudziak et al., US Patent 5,770,195, and Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or Carmichael et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or Tsai et al., Cancer Research Vol. 56, pages 794-801, 1996, and further in view of Maier et al., Cancer Research, Vol. 51, pages 5361-5369, 1991, or Lewis et al., Cancer Immunol. Immunother, Vol. 37, 1993, and Van Moorsel et al, Seminars in Oncology, 42/2, Suppl 7, S717-S723, 1997, or Hansen, Ann Oncol., Vol. 7, Suppl. 1, pp29, 1996. In view of the amendment to claim 1, the claimed inventions are obvious over the prior art.

In previous responses, applicant has argued that the claimed inventions are patentable over the prior art because one could not have predicted the safety and efficacy of the combination of an anti-ErbB2 antibody and gemcitabine; because the combination of an anti-ErbB2 antibody and gemcitabine does not exhibit the side effects that occur with the combination of HER2 and anthracycline; and because the combination of an anti-ErbB2 antibody and gemcitabine results in a synergistic effect of inhibiting tumor growth.

Applicant's arguments are not persuasive. The prior art teaches that treatment with either anti-ErbB2 antibodies or gemcitabine are safe and efficacious treatments (see above). Therefore, one of ordinary skill in the art would expect that the combination of the two treatments would be safe and efficacious. The prior art teaches that anthracycline derivatives can produce cardiac

toxicity (Singal et al, J. Mol. Cell Cardiol., 27: 1055-1063, 1995; cited in previous Office actions). Furthermore, even if the prior art fails to teach that the combination or an anti-ErbB2 antibody and an anthracycline derivative results in increased cardiac toxicity over the toxicity seen with an anthracycline derivative alone, one of skill in the art would not need to know this to be motivated to choose gemcitabine as a chemotherapeutic agent to combine with an anti-ErbB2 antibody. Because the safety and efficacy of gemicitabine is taught in the art, and because the general concept of combining anti-ErbB2 antibodies with chemotherapeutic agents is taught in the art, the motivation to combine the two treatments is provided by the prior art. A motivation provided in a rejection of a claim as unpatentable over the prior art does not have to be the same as the motivation supplied by the specification. Lastly, a synergistic effect resulting from the combination of two treatments, both known to be useful for the treatment of the same condition, is not in and of itself a surprising result, unless there is a teaching in the prior art that teaches away from the combination of two treatments.

A showing of an additive effect or even synergy is not sufficient to overcome a prima facie case of obviousness, if the results achieved were expected in view of the teachings of the prior art. See MPEP 716.02: "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." In re Corkill, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). In Corkhill, the claimed combination showed an additive result when a diminished result would have been expected. This result was persuasive of nonobviousness even though the result was equal to that of one component alone. Evidence of a greater than expected result may also be shown by demonstrating an effect that is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc.

v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L- aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.). Furthermore, the prior art teaches an example of a combination therapy involving an anti-ErbB2 antibody and a chemotherapeutic agent where the effect of the combination of the two treatments was synergistic (Hynes et al, above). Thus the demonstration post-filing that the combination of gemcitabine and an anti-HER2 monoclonal antibody exhibits synergistic anti-tumor effects is not sufficient to overcome the rejection, because it would be expected that the combination of HER-2 with gemcitabine would exhibit synergistic cytotoxicity.

Lastly, the specification confines its examples to inventions comprising the use of one species of anti-Her-2 antibody. Therefore, even if applicant were to provide evidence of surprising and unobvious results, this evidence would have to be commensurate in scope with the scope of the claims, which are currently drawn to methods comprising the use of any anti-Her-2 antibody.

Claim Rejections Maintained:

10. The rejection of claim 37 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for the reasons of record. The basis for this rejection is that the specification lacks an adequate written description of methods where an anti-ErbB2 antibody and gemcitabine are co-administered, and where the effective amounts of the anti-ErbB2 antibody and gemcitabine are lower than if the two agents had been administered as single agents.

Applicant's arguments have been considered, but are unpersuasive. Applicant points to passages referring to the general concept of synergism between an anti-Her-2 antibody and a chemotherapeutic agent, but fails to point to specific teachings that teach that applicant was in possession of the claimed invention of a method comprising the specific combination of an anti-Her-2 antibody, where the effective amounts of the anti-ErbB2 antibody and gemcitabine are lower than if the two agents had been administered as single agents. The specification fails to teach any examples of such amounts, and the one example provided in the specification (which does not include a method comprising the use of gemcitabine) does not appear to be an example of a synergistic combination, and does not apprise one of the amounts that one could use to make the claimed method. Therefore, the rejection is maintained.

The specification contemplates generally the concept of synergism between a chemotherapeutic agent that is not an anthracycline and an anti-ErbB2 antibody (support in original claim 12), but fails to supply support for the concept of synergism between gemcitabine

and an anti-ErbB2 antibody. The support for combining gemcitabine with an anti-ErbB2 antibody in a method for treating cancer is only supported by the mention of gemcitabine in a laundry list of chemotherapeutic agents. There are no teachings or even contemplation that the specific combination of gemcitabine and an anti-ErbB2 antibody in a method for treatment, where the amounts of each agent is less than the amounts of each agent when administered singly. While it may not be surprising that synergism may occur, and, therefore, a method as claimed could be made, the specification does not present evidence that applicant was in possession of the claimed invention at the time of filing. The one example provided by the specification concerning chemotherapy in combination with an anti-ErbB2 antibody fails to demonstrate synergism. Thus, the specification lacks even one example for the general concept synergism, and therefore, fails to provide any support for the specific combination of gemcitabine and an anti-ErbB2 antibody.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
December 29, 2003

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